(adalimumab) of Abbott, and that there are others being studied and/or in clinical trials, including some p38 MAPK inhibitors.

Applicants additionally attach abstracts from PubMed that provide insight into the treatment of rheumatoid arthritis and its relation, i.e., nexus, to p38. For example, see Badger, A.M. et al. (1996) Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function. J Pharmacol Exp Ther 279, 1453-1461, which reference predates the current application, and found that SB 203580 is a selective cytokine suppressive binding protein/p38 kinase inhibitor, and that it possesses therapeutic activity in collagen-induced arthritis. The remaining references attached, postdate the application, but provide further support on the art-recognized relation of the inhibition of p38 and the treatment of rheumatoid arthritis. See, for example, Jackson, J.R. et al. (1998) Pharmacological effects of SB 220025, a selective inhibitor of P38 mitogen-activated protein kinase, in angiogenesis and chronic inflammatory disease models. J Pharmacol Exp Ther 284, 687-692; Badger, A.M. et al. (2000) Disease-modifying activity of SB 242235, a selective inhibitor of p38 mitogen-activated protein kinase, in rat adjuvant-induced arthritis. Arthritis Rheum 43, 175-183; Wadsworth, S.A. et al. (1999) RWJ 67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase. J Pharmacol Exp Ther 291, 680-687; McLay, L.M. et al. (2001) The discovery of RPR 200765A, a p38 MAP kinase inhibitor displaying a good oral anti-arthritic efficacy. Bioorg Med Chem 9, 537-554; Kumar S et al. (2001) IL-1- and TNF-induced bone resorption is mediated by p38 mitogen activated protein kinase. J Cell Physiol. 187, 294-303; Suzuki M et al (2000) The role of p38 mitogen-activated protein kinase in IL-6 and IL-8 production from the TNF-alpha- or IL-1beta-stimulated rheumatoid synovial fibroblasts. FEBS Lett. 465, 23-7.

Thus, a nexus between the activity of the compounds and the claimed methods is more than adequately established in the specification and is more than adequately recognized by those of ordinary skill in the art. Thus, a person of ordinary skill in the art would not question the usefulness of a compound that inhibits p38 to treat rheumatoid arthritis.

Additionally, as the Office Action admits, applicants also provide a showing in the application that 38 specific compounds of the invention are effective at inhibiting p38.

Applicants thus provided an enabling disclosure in accord with the requirements of section 112, first paragraph.

Nevertheless, the Office Action alleges right up front that "there is no indication that inhibition of p38 invariably inhibits each of the cytokines listed (as each are simply

examples), nor is there any indication that the inhibition of p38 would invariably lead to the treatment of rheumatoid arthritis," see page 4 of Office Action, and that "a link between TNFα production and rheumatoid arthritis doesn't mean that any inhibition of TNFα would treat the rheumatoid arthritis." (Applicants note, as a side issue, that the claims do not require that p38 inhibit each of the cytokines listed, nor is treatment "invariably" claimed. The independent claims, for example, do not limit the treatment by any mechanism.)

No evidence has been presented to support the allegation that not every inhibitor of p38 will treat rheumatoid arthritis. In addition, it is not necessary for the claimed invention to provide invariable treatment to satisfy the requirement of 35 U.S.C. § 112, first and second paragraph. See, for example, *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, 224 USPQ 409 (CAFC 1984), *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46 (CCPA, 1974), *In re Geerdes*, 180 USPQ 789 (CCPA, 1974), *Ex parte Janin*, 209 USPQ 761 (POBA 1980). A claim may encompass inoperable subject matter, i.e., "it is not a function of the claims to exclude all inoperative embodiments."

The Office Action also alleges that "there is no evidence that the compounds actually treat rheumatoid arthritis."

(1) Evidence has been provided in the form of assays which show that the claimed compounds inhibit p38 activity. This is more than sufficient to demonstrate the compound will treat rheumatic arthritis.

(2) In addition, neither indications of invariable treatments or actual treatments are required in a patent application to enable an invention directed to a method of treatment of a disease. Instead, The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention

possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

With respect to the adequacy of the showing, laboratory data provided is more than adequate to satisfy the statute. Such data is the art-accepted marker of potential treatments, and is adequate for patentability. In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), the Federal Circuit stated that

> in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

The Office Action raises the issues of possible "side effects," "serious toxicity," "drug-drug interactions" and "significant adverse consequences." Applicants submit that these are safety issues which have nothing to do with whether the claimed method, satisfies the requirement of 35 U.S.C. § 112. Side effects, serious toxicity, drug-drug interactions, and significant adverse consequences are safety issues, which are independent of whether the compounds exhibit the activity claimed. These safety issues are left up to the Food and Drug Administration and not to the Patent and Trademark Office. The courts have repeatedly noted that the patent and drug-approval processes are distinct. See, for example, *In re Watson*, 186 USPQ 11 (CCPA 1975), *Scott v. Finney*, 32 USPQ2d 1115 (CA FC 1994), *In re Jolles*, 206 USPQ 885 (CCPA 1980), and *In re Anthony*, 162 USPQ 594 (CCPA 1969).

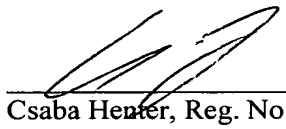
The Office Action also alleges that "one of ordinary skill in the art would be forced to perform and exhaustive search." Applicants respectfully disagree. The compounds of this invention have been clearly defined and methods for determining their activity have been provided in the specification and are known in the art. Determining the activity of the compounds in the claims is not undue experimentation in the field of pharmaceuticals, but rather an industry wide acceptable routine amount of testing. As discussed in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicants provide specific guidance as to how the claimed compounds can be tested for activity levels and actually provide data for 38 compounds. Additionally, those of ordinary skill in the art, as supported by the vast amount

of prior art in this area, know how to proceed in view of the disclosure. While the amount of work may require considerable effort (although not admitted), no undue experimentation is required.

For the foregoing reasons, reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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